Table 2 Intravenous mannitol in cerebral malaria

Citation	Study group	Study type (level of evidence)	Outcome	Key results	Comments
Newton *et al* (1997)	23 Kenyan children with confirmed *Plasmodium falciparum* cerebral malaria had intracranial pressure monitored. The 14 with severe and intermediate intracranial hypertension received intravenous mannitol	Uncontrolled clinical trial	Intracranial pressure Neurological outcome or mortality	Mannitol lowered the intracranial pressure in all children Of the 4 children with severe intracranial hypertension, 2 died and 2 had severe neurological sequelae. Of those with intermediate intracranial hypertension, all survived. 8 had a good outcome, 1 developed hemiparesis, and 1 learning difficulty	Primary focus of study and outcome measured was measurement of intracranial pressure in cerebral malaria

CLINICAL BOTTOM LINE

- There are no controlled data supporting the use of mannitol for cerebral malaria. Consensus statements should be followed.

Intracranial hypertension as a feature of cerebral malaria probably contributes to the poor neurological outcome and death of many children with *Plasmodium falciparum* malaria. A likely cause is an increase in cerebral blood volume due to sequestered parasitised erythrocytes. Mannitol is a relatively cheap osmotic agent which appears to lower intracranial pressure. This may potentially improve the survival and neurological outcome of many children with cerebral malaria. Anecdotal evidence suggests that the conscious level of children with cerebral malaria improves with intravenous mannitol; however, when it should be used is unknown. The benefit may only be temporary; however, in resource limited settings where intensive nursing care may not be optimal, shortening the duration of a coma may have benefits for neurological outcome.

The WHO emphasise that none of the ancillary treatments for cerebral malaria have sufficient supporting evidence to be used. No controlled study for the use of mannitol in paediatric or adult cerebral malaria could be identified and its use can not be recommended. Further studies are necessary to determine its value and potential side effects.

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Do antipyretics prevent febrile convulsions?

Report by
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A 1 year old child is admitted following their first febrile seizure (FS). We wish to prevent recurrences during further febrile episodes. The nursing staff ask you to prescribe an antipyretic. Later you come to advise the parents on methods of preventing further febrile seizures.

Structured clinical question

In children who have experienced a febrile seizure [patient] does prescribing antipyretics [intervention] reduce recurrences of febrile seizures [outcome]?

Search strategy

Secondary sources

Cochrane Library and DARE—"febrile convulsions/seizures and antipyretics", "febrile convulsions/seizures and paracetamol", "febrile convulsions/seizures and ibuprofen"; one systematic review found (paracetamol for treating fever in children); two protocols.

Prodigy Evidence Based Clinical guidance—"febrile convulsions"; nil relevant found.

Primary resources

Pubmed clinical queries (1966 to Jan 2003): "antipyretics and febrile convulsions"—80 references. Of these, three were randomised controlled trials but one was irrelevant (investigating antipyretic effects rather than subsequent seizure reduction).

Commentary

As the essential precursor of a febrile seizure is a fever, physicians and paediatric nurses have concluded that antipyretic measures should prevent febrile seizures. Antipyretics continue to be among the most commonly prescribed medications, especially for children at risk of such seizures. Parents are usually advised that the administration of antipyretics to at risk children may reduce the risk of further convulsions. When asked, the majority of medical trainees and paediatric nurses in our unit replied that the reason for giving paracetamol to children who were at risk of febrile seizure recurrence was to prevent further convulsions. However, the evidence suggests that antipyretics have no effect on preventing further febrile seizures. At this hospital, 13% of children admitted with their first FS subsequently developed repeated FS soon after admission despite the routine administration of paracetamol to control fever prior to the seizure.[1]

Children with high risk of recurrences of FS (complex features of FS, family history of FS, age less than 1 year, low grade fever at the onset of FS) develop recurrences in at least 80% while those without these risk factors rarely develop recurrences. Antipyretics are used for both groups of children, suggesting that it is these risk factors, and not antipyretics, which are the crucial determinants of the risk of recurrence.

Controlled studies of antipyretic medications, given during the original acute illness following a febrile seizure or during subsequent febrile episodes have failed to show a preventive effect in children at risk of FS (table 3). A randomised, placebo controlled trial in children at risk of FS found no evidence that paracetamol, with or without diazepam, was effective in preventing FS during subsequent febrile episodes.[2] A second

Table 3 Antipyretics in febrile seizures

Citation	Study group	Study design (level of evidence)	Outcome	Key result	Comments
Uhari *et al* (1995)	180 children after first febrile seizure randomised to 4 groups: a) placebo + placebo b) placebo + paracetamol c) diazepam + paracetamol d) diazepam + placebo	Randomised double blind placebo controlled trial (level 1b)	Number of recurrence of FS	a) 14 (25.4%) b) 9 (16.4%) c) 14 (25.5%) d) 18 (32.7%) (no statistical difference)	Duration of follow up: two years
Schnaiderman *et al* (1993)	104 children after first febrile seizure randomised to two groups: a) paracetamol 4-hourly b) paracetamol as required	Randomised controlled trial (level 1b)	Early recurrence of FS	a) Regular paracetamol = 4 (7.5%) b) PRN paracetamol = 5 (9.8%) (p = not significant)	In hospital only (no follow up)
Van Stuijvenberg *et al* (1998)	230 children after first febrile seizure randomised to: a) ibuprofen (n=111) b) placebo (n=119)	Randomised double blind placebo controlled trial (level 1b)	Number of recurrence of FS	a) 31 (35.7%) b) 36 (33%) (p = not significant)	Mean duration of follow up 1.04 y
Von Esch *et al* (2000)	Treatment group with: a) ibuprofen or paracetamol (n=109) b) no antipyretics (n=103)	Non-randomised controlled trial (level 2a)	Number of recurrence of FS	Recurrence risk per fever: a) 6.3% (treatment group) b) 12.2% (control group) ARR = 5.9%; (95% CI: –0.2% to 12%)	
Meremikwa *et al* (2002)	RCTs with paracetamol compared to placebo	Systematic review (level 1a)	Number of recurrence of FS	Conclusion: no evidence that paracetamol is effective in preventing FS	

CLINICAL BOTTOM LINE

- There is no evidence that antipyretics reduce the risk of subsequent febrile convulsions in at risk children.
- Prescription of paracetamol following febrile seizures may provide comfort and symptomatic relief, but should not be recommended to prevent further febrile convulsions.

randomised trial compared the antipyretic effectiveness of paracetamol administered at regular intervals (group 1) versus paracetamol administered at the time of fever (group 2) in children presenting with an FS. Early recurrences of FS (within the first 24 hours) were similar in both groups.[3] Ibuprofen was also evaluated in a randomised, double blind, placebo controlled trial in children at risk of FS. The recurrence rate was similar in both groups.[4] In another open trial, children at risk of FS were offered either ibuprofen or paracetamol during subsequent febrile episodes or else no medication. The recurrence risk of FS was similar in all groups.[5] These four studies concluded that the antipyretics paracetamol and ibuprofen had no preventive effect on the recurrence of FS. A recent review[6] of trials assessing the effects of paracetamol on the clearance time of fever and on FS identified 12 randomised or quasi-randomised controlled trials. It concluded that the trials failed to show any convincing evidence that paracetamol is effective in reducing fever or preventing FS.

While antipyretics may have a role in improving comfort and general wellbeing, we should surely not be advocating medication for purposes that have been shown not to work.

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The duck-yak problem. Illustration by Jack Maypole, MD